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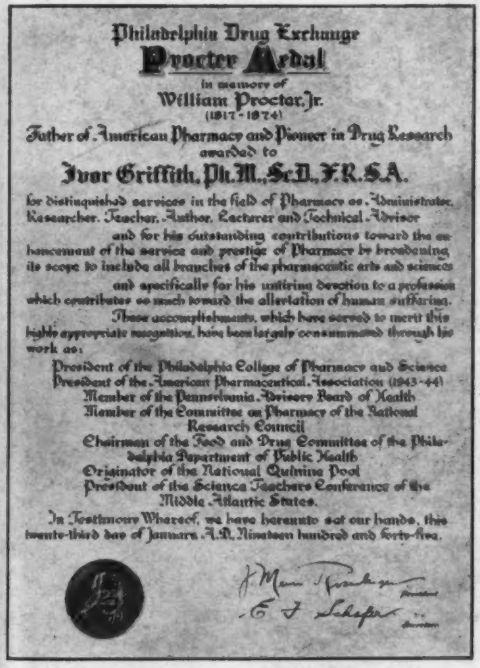

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(1817-1874)
Father of American Pharmacy and Pioneer in Drug Research
awarded to
Ivor Griffith, Ph.M., Sc.D., F.R.S.A.

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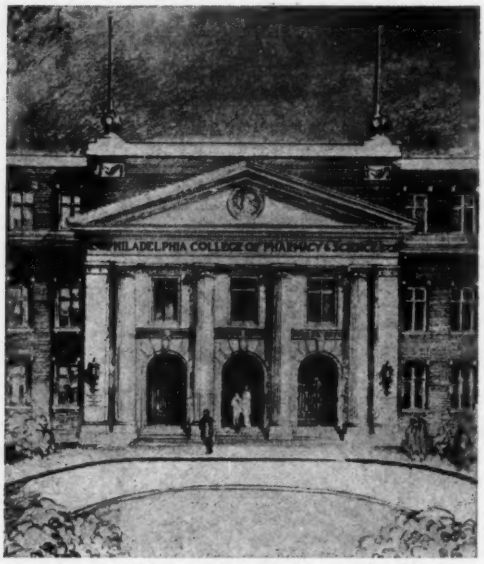

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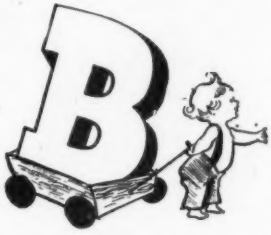

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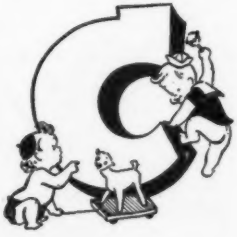

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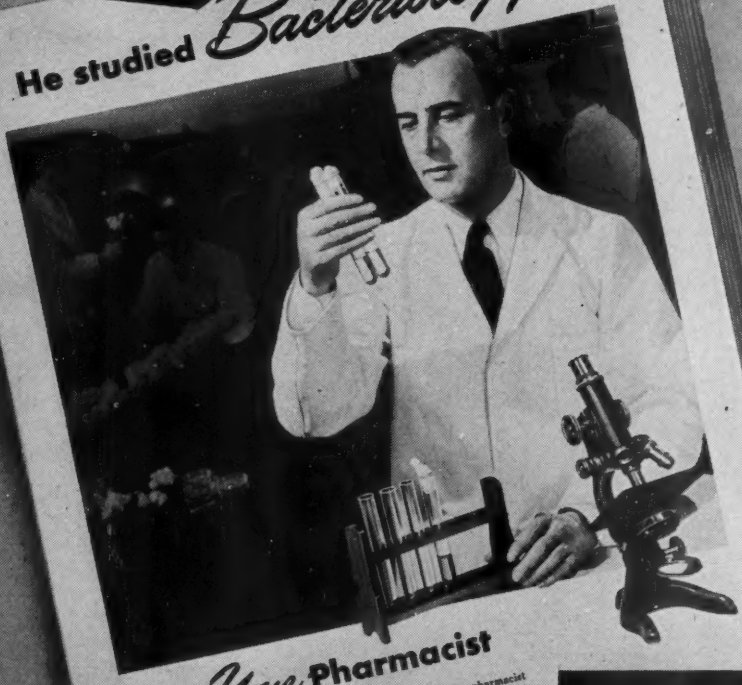

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OUR COVER

THE PROCTER MEDAL

WILLIAM PROCTER, JR., was a Philadelphia Quaker whose teaching and writings in Pharmacy during the early nineteenth century brought to him the title of "Father of American Pharmacy". He contributed more than half a hundred scientific papers to the literature of his time, as well as editing this JOURNAL from 1850 to 1871. He was professor of pharmacy at the Philadelphia College of Pharmacy, and one of the founders of the American Pharmaceutical Association. His accomplishments as the proprietor of a drug store in Philadelphia are legion.

With this background in mind, it was quite fitting that the inaugural Procter Award, a gold medal and a scroll, sponsored by the Philadelphia Drug Exchange, go to Dr. Ivor Griffith, president of the Philadelphia College of Pharmacy and Science. Like Procter, Dr. Griffith has been professor of pharmacy at the College, editor of this JOURNAL, and contributor of many scientific papers. He, too, has engaged in the practice of pharmacy in many of its aspects.

The award was made at a dinner given at the Bellevue-Stratford Hotel on January 23, 1945, on the occasion of the eighty-fourth anniversary of the founding of the Philadelphia Drug Exchange, the oldest drug trade body in the United States. Further awards of the Procter medal are planned by the Philadelphia Drug Exchange to those who by outstanding achievement warrant this high and distinguished honor.

EDITORIAL

POST-WAR SUPPLIES OF PLASMA

ONE of the truly great advances in therapy brought about by wartime conditions has been the use of human plasma and its fractions in the many conditions for which it is almost a specific. Were it not for the tremendous amount of blood that has been donated by patriotic citizens coupled with the Navy's demand for serum albumin, the great technical advances in plasma fractionation accomplished in the last few years might never have been achieved. With large quantities of specific plasma fractions thus available their medicinal uses were investigated more fully with the result that they have become firmly established as irreplaceable products in modern medical and surgical practice.

With the conclusion of the war a very real problem will arise in that the patriotic urge to donate blood will be at an end and the thousands who regularly contributed this invalauble aid to our servicemen will no longer be motivated by self-sacrifice. If an attempt is made to obtain donors by financial inducement the cost of plasma products will be beyond the reach of many persons who need such therapy and it will be made worse by reason of the fact that diminished production will greatly increase unit cost. How then can healthy human blood be obtained for the preparation of plasma, serum albumin, fibrin film, fibrin foam, etc.? The proposal that it be obtained from persons immediately after death is not of particular moment since this procedure is fraught with great technical difficulties as well as emotional barriers erected by the relatives of the deceased.

We would like to propose a means of collecting blood which is sound from the medical, economic and sociological standpoint. Why not obtain it by the voluntary contribution of inmates of federal, state, and county prisons? A plan could be devised as follows: Any inmate voluntarily subscribing to the plan would receive for each donation a credit on his prison term together with special privileges

and even food paid for in part by the money collected by the prison for the donated blood. The plan would of strict necessity be voluntary for each individual and it could be discontinued at any time. Collections of blood would not be so frequent as to impair the health of the donor, and proper medical supervision would be given him at all times.

The sociological aspects of this plan are of interest since actually a convict who was committed to prison for having violated the rules of organized society could now partially repay his debt to society with his blood, a much more reasonable payment than his life! The feeling that one was actually helping others and yet at the same time helping oneself might even be expected to develop a sense of responsibility in many otherwise irresponsible persons. The individual by seeing motion pictures of persons saved by his blood would have the importance of his contribution impressed upon him.

This plan would have to be instituted carefully and fully explained to the prospective donors. Even then many would be suspicious and refuse to cooperate; but as they saw donors thrive and receive special benefits and reduction of sentences, their prejudice would disappear. Eventually all healthy inmates would endorse the plan. The administration of this project would require enlightened, fair-minded persons since if it were improperly handled in any prison it could do great harm to the morale of the prisoners. Their confidence would have to be won and maintained and this is not a job for some of the old-time prison guards and wardens who consider their wards only with contempt.

In proposing this idea we can see not only a means of collecting blood for medicinal uses but also a forward step in the handling of prisoners in such a manner as to improve their moral and social outlook. This should be the primary objective of any prison program, not simply one of confinement and punishment.

It is at least worthy of consideration by those who will eventually seek a source of supply of human blood.

L. F. Tice.

PROGRESS OF OUR KNOWLEDGE OF BLOOD PROTEINS AND OF THEIR THERAPEUTIC VALUE [1]

By Edwin J. Cohn, M. D.[2]

RECOGNITION of the role of the National Research Council in making available to Government agencies the knowledge and advice of civilian experts in the medical sciences appears to be peculiarly appropriate at this time. I am honored to have been asked to participate in this ceremony, and to discuss blood proteins and their therapeutic value. The Blood Substitutes Sub-Committee of the National Research Council is a small group, the membership of which has changed but little from the time, many months before Pearl Harbor, when it was reorganized and charged with the responsibility of advising the armed forces and Government agencies as to the methods to be employed and the products to be accumulated against military emergency or civilian disaster. Although it has carefully and critically examined the properties of every blood substitute that has been suggested, it has thus far recommended only products derived from human blood. Its membership has included the expert who recommended the methods for blood procurement on the basis of which the American Red Cross blood donor program has functioned so successfully; the expert on blood banks, who continuously stressed the place of whole blood in therapy; the expert on dried plasma whose knowledge and experience of many years in its preparation and administration have thus always been available; a professor of medicine; a professor of surgery; and myself, a chemist concerned with the properties of proteins, their separation and purification, and their biological functions.

These experts have met repeatedly with the designated representatives of the Surgeons General of the Army, the Navy, and the Public Health Service, the Red Cross, the Office of Civilian Defense and the Food and Drugs Administration, inviting other experts to meet with them as occasion demanded and, unburdened by an admin-

[1] Address given before the American Pharmaceutical Manufacturers' Association, at Waldorf-Astoria, New York, December 11, 1944.

[2] Department of Physical Chemistry, Harvard Medical School.

istrative hierarchy, or intermediaries, have transmitted their advice directly and supplemented and implemented their recommendations with reports and memoranda on the value and safety of products and of chemical or biological processes. This is the form of civilian advisory function which President Lincoln envisaged in creating the National Academy of Sciences and it is to be hoped that it will be the form of the agencies which will advise Government regarding the medical sciences in the post-war world.

Whole Blood. You have asked me to discuss "Progress in Conquest of Knowledge of Blood Proteins and of Their Therapeutic Value". Implied in this title is the question as to how much of the organization for the collection and processing of the human blood, that has been developed during this war, will continue in the post-war world. Whole blood and plasma were well known therapeutic remedies before this war. Their value has been further proven in military theaters of operation. Whole blood is especially needed when there has been severe blood loss, or when major operations are to be performed in which severe blood loss is anticipated. The red cells which are responsible for the respiratory function of the blood, carrying oxygen to the tissues, are also needed to combat the anemia which frequently occurs in convalescence from wounds. The therapeutic value of the red cells is thus related to their physiological functions. The therapeutic value of other constituents of blood may also be related to their physiological functions.

The lability of whole blood made it necessary to prepare for this war by the accumulation of reserves of the more stable components of blood. However, work continues in many laboratories in an attempt to increase the span of life of the labile cellular constituents of blood so as to render them available over longer periods of time. Progress in the preservation of red cells both in whole blood and in media in which they can be resuspended may be expected to continue at an accelerated rate because of the methods that are being developed and the knowledge that is being gained.

Many of the conditions for which whole blood transfusions are used, notably where there is a need for the red blood corpuscles, can probably be successfully provided for by resuspended red cells. Others may be satisfied by the injection of plasma or of a plasma fraction. The longer life of the red cell in whole blood than resuspended in any medium at present known makes it necessary whenever possible to

fly whole blood to our armed forces. The social economy of using cells and plasma separately in the therapy of different conditions, if either can be demonstrated to be as satisfactory as the whole for the conditions indicated, is, however, so advantageous as to demand consideration in the post-war world.

Plasma. The separated plasma can be stored in the liquid state, can be frozen, or can be dried from the frozen state. In the liquid state it retains its colloidal properties necessary for the treatment of shock, but the more labile components of plasma, the prothrombin and fibrinogen, concerned with blood coagulation, complement and the antibodies concerned with immunity deteriorate with time. For an economical civilian program, therefore, liquid plasma has distinct limitations. In the frozen state, the labile components of plasma are better preserved; here the limitation is the inconvenience for storage and transport and immediate emergency use. In the dried state, most of the labile components of plasma are preserved. Dried plasma has been used by our armed forces; and processed to a stable state from the blood collected by the American Red Cross it, as other dried products, can be accumulated as a reserve against need at a future time and place.

Plasma was accumulated in this war largely for the prevention and treatment of shock. Shock as observed in military medicine generally results from a rapid decrease in the volume of circulating blood due to the loss of blood and plasma proteins externally and into damaged tissues. It is most frequently treated or prevented by injection of plasma proteins. The injected proteins insofar as they cannot readily pass through the kidney increase the body's reservoir of plasma proteins, and insofar as they do not readily traverse the capillary walls, increase the plasma volume by drawing water from the tissues into the blood stream. The function of controlling the equilibrium between the water and the electrolytes in the blood and in the tissues is largely performed by the smaller proteins of the blood stream, known as the albumins, although all dissolved colloids will, of course, exert some osmotic effect.

Albumin. The albumins of plasma represent less than 60 per cent of the plasma proteins but are responsible for nearly 80 per cent of the osmotic efficiency of the plasma, upon which its value in the treatment of shock largely depends. Human serum albumin has also

been recommended by the Blood Substitutes Sub-Committee to the armed forces and, like plasma, it has been processed in large amounts from the blood collected by the American Red Cross. Unlike plasma, albumin is so stable that it can be dispensed in solution; the albumin molecules are so symmetrical that a 25 per cent solution is iso-viscous with whole blood. The isoelectric, salt-free albumin is prepared as a dry, white powder; it can be redissolved at any concentration and with any diluent. As a concentrate poor in salt, it is proving of value as a diuretic agent. In the treatment of shock, it functions as does plasma, largely by virtue of the albumin it contains, by pulling water back into the blood stream, and holding it there. This results in a decrease in viscosity and a restoration of the volume of circulating blood to normal, so that oxygen is transported to the tissues and the other physiological functions of blood are resumed.

Although traumatic shock occurs frequently enough in civilian life, as a result of automobile, industrial or other accidents, to warrant a peace-time society making provision for its prompt treatment with adequate supplies of plasma or plasma derivatives, the control of certain infectious diseases with plasma derivatives appears to offer at least as great an opportunity for civilian medicine.

Gamma Globulins. A large scale public health experiment has now demonstrated the value in the modification or prevention of measles of the gamma globulin of the human plasma, separated from the same plasma as yielded the albumin employed in the prevention and therapy of shock. Of the plasma proteins about 58 per cent is albumin and 11 per cent gamma globulin. Two fractions of gamma globulin may also be separated, the one richer in euglobulin and the other (Fraction II) in pseudoglobulin. The latter fraction has thus far been employed in the study of the control of infectious diseases and represents approximately 5 per cent of the plasma proteins. None the less gamma globulin may come to be recognized as the most important fraction of the plasma from the point of view of public health.

Pooled normal or convalescent plasma has long been used in the control of certain infectious diseases. Many of the antibodies to the variety of infectious diseases to which the population contributing the blood has been exposed are gamma globulins. Moreover it has been possible to demonstrate that a population shows heightened immunity following an epidemic of a special disease. The concentration of

gamma globulin antibodies over the pooled plasma thus far achieved by fractionation is approximately twenty-five-fold if we compare plasma with the concentrated solution of gamma globulins being made available to the armed forces and, through the Red Cross, to public health agencies. As a result, titers of certain antibodies, though not necessarily of all, are comparable to those of the corresponding convalescent sera. Therefore, in the prevention or treatment of any disease where the value of convalescent serum has been demonstrated, the effectiveness of a concentrate from pooled normal plasma should be investigated. If convalescent serum, or hyper-immune serum is fractionated, still higher antibody titers may be obtained in the concentrated gamma globulins.

The antibodies effective in the modification or in the prevention of measles are present in the more soluble fraction (Fraction II) of the gamma globulins. This is true also of the antibodies for several other virus diseases. Effective use of the gamma globulins in the control of diseases other than measles has been reported. Should these preliminary studies be substantiated by large scale military or public health investigations, the need for gamma globulin may prove even greater than has thus far been anticipated. None the less it should be stressed that in the case of many diseases those bearers of immunity which are the antibodies of the blood stream cannot be made available in amounts large enough, or injected soon enough, to prevent the onset of disease. In others, the incidence of the disease in susceptibles is so small that it would be necessary to immunize passively an entire population in order to offer protection to the one in a thousand who might contract the disease. The blood donors for such an undertaking might not always be available whereas blood donors conscious of the contribution that they were making to the control of other diseases could clearly always be counted on in a society which has contributed as has ours to the blood donor program.

Two problems which are chemical, rather than clinical, have thus far limited studies to determine the most effective use of the gamma globulins. The progress that is being made, however, suggests that both are yielding to systematic scientific investigation. The first is concerned with the removal of depressor substances which have heretofore prevented the intravenous use of gamma globulin concentrates. Conditions for the separation of these substances and thus of the preparation of gamma globulins safe for intravenous use appear

to have been found, however, and appraisal of the value of gamma globulin intravenously injected in diseases where larger amounts may be needed than can conveniently be administered intramuscularly has been begun. Intravenous injections of 25 cc. have been given to small children with acute infections without reaction and 50 cc. to children not acutely ill. The injection of a concentrate of gamma globulin equivalent to the amount which could be introduced as plasma or whole blood only by replacing the entire blood volume by transfusion would thus appear to be both possible and practicable. Chemical specifications for the routine production of such preparations are, however, not yet completely satisfactory.

The second chemical problem concerns the separation of the gamma euglobulins of the plasma (in Fraction III-1 from the iso-agglutinins (blood typing globulins), cholesterol and carotenoid bearing betaglobulins, so that clinical investigations with this potential source of antibodies may also be begun. The O typhoid agglutinin has been found concentrated in this fraction rather than in Fraction II. The possibility exists, however, that sub-fractionations of the gamma globulins may yield, in time, products derived from the same plasma, some of which are more potent concentrates of certain antibodies; some of others.

*The fractionation process** that we have developed yields all of the components of human plasma in five major fractions. The number has purposely been made as small as possible so as to facilitate and render economical large scale processes. We shall not stop here to discuss the physicochemical systems upon which the separations depend except to state that it is an extension to proteins of the principles determining electrostatic interactions with neutral salts, which

* The program of plasma fractionation which has been developed in this laboratory was originally supported by grants from the Rockefeller Foundation and from funds of Harvard University. It was aided early in 1941 by grants from the Committee on Medicine of the National Research Council, which included a grant from the American College of Physicians. Since August, 1941, it has been carried out under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University. The insight of many fellow workers in this department has been immeasurably aided by many colleagues—chemical, clinical, immunological and pathological—members of this or other Universities, of the Armed Forces, of Committees of the National Research Council, of the American Red Cross, or of the commercial laboratories with Navy contracts for plasma fractionation, who labored with us. Indeed, it would be impossible to list here the very large number of individuals and agencies who have collaborated in this work.

generally lead to increased solubility, and interactions with less polar organic liquids, which generally lead to precipitating action. The balance between these forces has made possible the definition of conditions leading to far sharper separations than have previously been possible. The theory and general methods, though not the detailed procedures, are equally applicable to plasma and tissue extracts of plant or animal origin, that is, to all systems in which a large number of protein and lipid components are to be separated from each other and without loss of the biological activity upon which their therapeutic value depends.

As applied to plasma, the fibrinogen, which is the structural element of the blood clot, is concentrated in Fraction I. Fraction II+III contains essentially all of the prothrombin, which converted to thrombin transforms fibrinogen into fibrin; all of the immune globulins for which tests have been carried out; the isohemagglutinins and Rh antibodies, of value in blood grouping, as well as all of the carotenoids and such part of the cholesterol and phosphatides of plasma as appear to be associated with beta rather than alpha globulins; the midpiece of complement, and probably innumerable other components of plasma which are not yet recognized by virtue of their chemical or biological properties. The remaining globulins are concentrated in Fraction IV.

Isohemagglutinins have also been prepared under contract with the Navy because of the value of these by-products of plasma fractionation in the grouping of whole blood. The products that have thus far been prepared commercially have been fractionated respectively from pools of A or of B plasma. Since there are roughly four times as many A as B donors in our population, this discrepancy introduces an uneconomical factor in the typing of globulins from human plasma. Recently one of my colleagues has suggested and demonstrated the value of another method of segregating the plasma in pools for the preparation of blood grouping globulins. In this method the small number of B bloods are used only to absorb the A anti-B agglutinins from O blood. The resulting fractionated and purified isoagglutinins are not only group specific but are far more avid with respect to the B anti-A_2 and A_2B sub-groups than the B anti-A agglutinins prepared from B plasma. And, of course, from five to eight times as much of the product is obtained from the same number of grouped bloods. This process thus makes available an almost equivalent

amount of B anti-A and of A and anti-B grouping material and greatly increases the economy of the preparation of these highly potent blood grouping globulins.

The alpha and beta globulins concentrated in Fraction IV have recently been subdivided into two fractions, both sufficiently stable to be dried from the frozen state and reconstituted as clear soluble protein concentrates. One of these sub-fractions (IV-1) contains the remaining lipids of the plasma which, in this preparation, appear to be associated with alpha globulins; largely with alpha$_1$ globulins. The remainder of Fraction IV, tentatively designated IV-3, 4, is almost free of lipids, though rich in alpha and beta globulins and is subject to further sub-fractionation in the interest of concentrating and purifying the diverse components which it contains.

In this process, all of the proteins in plasma concerned with the coagulation process are concentrated in Fractions I and III-2; the immune globulins in II and III-1; the lipo proteins in III-1 and IV-1 and the albumin in Fraction V which represents approximately 50 per cent of the plasma proteins. Since the albumin in this fraction makes by far the largest contribution to the colloid osmotic pressure of plasma, fractionation yields albumin to perform this function and other fractions to be employed in therapy in connection with more specific physiological functions.

Not only has Fraction II been prepared in a state safe for intravenous use in the last months, but so also has Fraction IV-3, 4. What are the physiological functions and what are the therapeutic uses of this large fraction rich in alpha and beta globulins, poor in lipids and antibodies and in components of the coagulation mechanism? The chemist is fulfilling his function when he makes these alpha and beta globulins available in soluble, stable and safe form for intravenous use. We can depend on our clinical colleagues, armed with these tools, to determine the functions of these substances in the economy of the body and to discover their uses in therapy.

Fibrinogen, Thrombin and the Uses of Fibrin Products. In the subfractionation of Fraction II+III to yield the gamma globulin antibodies in Fraction II, prothrombin is of necessity first separated in Fraction III-2. Prothrombin may be converted to thrombin with human thromboplastin and large amounts accumulated and made available as sterile dry powders ready for reconstitution and imme-

diate emergency use. For stopping the flow of blood, in surgical procedures, thrombin is the only component of the clotting mechanism which must be supplied. For the most effective use of thrombin in hemostasis, however, it must be applied with a matrix which can hold the thrombin in the bleeding area until clotting is completed. A porous matrix soaked in thrombin solution can accomplish this mechanical result. Fibrin foam is such a matrix formed from human fibrinogen and thrombin. It effectively controls bleeding from oozing surfaces and from veins, even very large ones. Though not recommended for brisk arterial hemorrhage, it has proved very effective in neurosurgery in controlling hemorrhage from the dura, from tumor beds, from dural sinuses, and from large cerebral veins. In general surgery it has been reported effective, in a small number of patients, in controlling hemorrhage from the cut surface of the liver and kidney, in jaundiced patients, in thoracic operations, and in stopping bleeding in hemophilia when other methods have failed.

In the dry state fibrin foam is a porous material composed of strands of fibers separated by air spaces of macroscopic size. It readily absorbs water, saline, or thrombin solution, and can be used in conjunction with a sulfa drug or with penicillin. The physical properties of the foam can be varied by controlling the conditions of manufacture. Since fibrin foam is prepared completely from human proteins and is rapidly absorbed with minimal tissue reaction, it may be left in place, thus preventing recurrence of bleeding. It is easily handled in the operating room, and, like serum albumin, is immediately available for use in emergencies.

Just as the asymmetry of certain synthetic polymers is responsible for the remarkable mechanical properties of industrial plastics, the fibrinogen molecule endows products of this human protein with remarkable mechanical properties. Among these products is fibrin film. Fibrin film may be prepared from fibrinogen and thrombin as a strong, rubbery sheet which can be stretched reversibly from two to three times its original length. This material can be made in various shapes and thicknesses, and in the form of seamless tubing. Its mechanical properties can also be varied from a soft, rubber-like elasticity to a parchment-like consistency.

The mechanical properties of the soft, rubbery films (as shown by their stress-strain curves) bear a marked similarity to those of the elastic ligament of the neck, the ligamentum nuchæ. The tough films

with delayed elasticity resemble rather wool or hair in their mechanical properties. It may be possible to imitate, with different types of fibrin products, still other natural structures of the body.

The fine structure of fibrin film has been shown to involve pores which in one type are of the order of 60 Angstrom units in diameter. Hemoglobin molecules in solution pass through these pores readily, but plasma globulins are partially and fibrinogen molecules completely retained.

The mechanical properties of certain types of fibrin films make them suitable for use as dural substitutes and in the prevention of meningocerebral adhesions. The duration of their persistence in the body can be adjusted by suitable treatments. They have been used in neurosurgical operations and appear to be an excellent material for these purposes, patients having been followed for as long as fifteen months without the appearance of unfavorable sequelæ. Other types of fibrin film and of fibrinogen plastics are being tested for other surgical applications.

Albumin and the immune globulins, fibrin foam and thrombin have been licensed under the National Institute of Health, and have been prepared in large amounts under contract with the Navy. Fibrin films, which were developed in our laboratory several years ago, presented a considerable problem as a satisfactory sterilization procedure adaptable to their large scale preparation remained to be developed. I am happy to be able to report that a satisfactory procedure in which the films are sterilized by steam in the final container has been developed and is making large numbers of films prepared in this way available for final appraisal.

In summary, the progress in the conquest of knowledge of blood proteins and their therapeutic value that has been gained in this war renders it possible to approach the future with a very different view than was available to the most far-sighted physician who was taking advantage of all scientific knowledge, especially that contributed by Landsteiner on blood grouping, a decade ago in arranging for safe blood transfusion from donor to patient.

In the past, repeated blood transfusions had, of course, often been administered but not to the extent that our British colleagues practised, using blood and serum banks, during the first years of this war. Their experience from such multiple transfusions indicated on the one hand the value, in certain conditions, of injecting large

amounts of plasma proteins, and on the other the need for red cells when such large amounts of serum proteins were administered.

The program of the American Red Cross has demonstrated the extent to which carefully controlled, centralized, collection and processing centers could contribute both to the safety of the donor, and to that of the recipient of one or another of the products prepared from the blood contributed. The record that has been achieved is a fine one and redounds to the credit of the American Red Cross and the laboratories of the pharmaceutical industry that have loyally collaborated in this nation-wide undertaking.

The need of multiple transfusions makes it necessary to use the blood contributed by a number of donors in treating a single casualty. Indeed, whether we are dealing with the colloidal properties of the plasma proteins in shock or with the immune properties of the gamma globulins—which contribute but little to the osmotic efficiency of the plasma—the therapeutic value of massive doses, under certain conditions, has become apparent.

The control of infectious diseases by passive immunization with gamma globulins may well be the largest need for a blood derivative of a civilian population and one to which a civilian population can be expected to contribute in the interests of the modification and control of a children's disease, such as measles, until such time as the immunity of the growing generation is achieved.

In the fractionation of blood to obtain the gamma globulins, the red cells and the proteins which they contain become available for the therapeutic uses for which they are needed; the albumin for the treatment of shock, hyperproteinemia, edema and—prepared in the salt-poor condition—as a diuretic agent; fibrin foam and thrombin as a hemostatic agent; fibrin film as a substitute for a natural body membrane and the large number of other cellular, protein and lipid components, whose physiological function and chemical nature are only beginning to be explored, for whatever therapeutic purposes may prove the most important.

Starting with the assumption, which must for the present remain an assumption, that every part of human blood performs an important natural function, we must continue, as we have begun, to make available as many as possible of its diverse cellular, protein and lipid components, separated and concentrated as specific therapeutic agents, of value in different conditions, in the interests of the most effective and economical use by a society of the blood which it contributes.

HOBBIES IN PHARMACY

By John E. Kramer, B. Sc.

HOW often have we heard the man with the eight-hours-a-day, five-days-a-week position say, "If only I had time to indulge in a hobby." Yet, many pharmacists, working fifty or more hours each week, find ample opportunity and time to do just that. In fact, the various phases of pharmacy offer to those within the realm of the profession an unusual number of outlets for the common, human urge to follow a hobby.

Pharmacy is defined as the science which treats of medicinal substances, comprehending a knowledge of medicines, their preparation and dispensing, their identification, selection, preservation, combination and analysis. As a profession, it has a heritage of 4000 years of written history and, it is confidently believed, much more that is not recorded. Many druggists pride themselves on their specialized knowledge of the vast history of their calling, and have assembled treatises, books, pictures, and other pieces of value from an historical standpoint. A number of books on the history of pharmacy have been written by men whose interests in that phase of the profession started as hobbies. We have special reference to such men as LaWall, Kremers, Urdang and others.

The lore of old and new drug jars and shelf-ware is intriguing, and many and valuable are the collections of such containers. Mortars and pestles and other pieces of apparatus, some of them once the tools of appointees to royalty, are now proud possessions of pharmacists who take delight in searching out and gathering together such rare and interesting pieces. Unusual show-globes have formed quite a few "hobby" collections. Old and historically valuable books form the nuclei of many a modern pharmacist's "five-foot book shelf." The pharmacopœias and the formularies, private and public, issued regularly in this and other countries for more than a century, and irregularly before that time, afford the amateur scientific book collector a wide and extremely interesting field in which to operate to his heart's content.

For the retail pharmacist who has a little plot of ground adjoining his store or his home, what could be more fascinating, and healthful, too, than the pastime of cultivating the ground and growing various medicinal plants from scattered and remote parts of the world, but which are all assembled eventually in his compounding room? Many of these drug plants are beautiful and decorative, while

others are desirable because of their agreeable odors. Commercial cultivation of such plants is, of course, not feasible in individual instances, but their value for display purposes and for a healthful hobby is inestimable.

Many corner drug stores, especially in the neighborhoods, are official sub-post offices. Most drug stores sell stamps as an accommodation to customers. In any case, the pharmaceutical philatelist is an oft-found person, invariably happy in his work of garnering corner blocks, first issues, rare post marks and other morsels so dear to the heart of the sincere stamp collector. In many countries, various plants and animals, from which medicinal substances are derived, are used in postage stamp designs. There have been a number of collections featuring such stamps made by pharmacists who have followed this line of relaxation.

In the days of the Civil War, and before, not only did postage stamps bear designs, but envelopes were printed with pictures, slogans and cartoons. Many of these were on pharmaceutical subjects, and the AMERICAN JOURNAL OF PHARMACY has, in the past few years, printed interesting stories about such wrappers written by Mr. George N. Malpass, whose knowledge in the field of philately arises from his interest in the subject as a hobby.

Recently, a young fellow whose dad owns a drug store developed a collector's passion for store labels, and his hobby was publicized in a trade journal, along with the request for other pharmacists to send samples of their labels to the boy. As a result he received more than a thousand contributions to his collection, and he will be happily engaged in arranging them according to his taste for many future pleasant evenings.

Pharmacists who indulge in the game of chess find much enjoyment in the play, and one has gone so far as to maintain an extensive collection of chess sets. Probably his proudest set is one which uses small-scale mortars, weights, flasks and other pharmaceutical ware to symbolize rooks, pawns and other chessmen.

There are many other foundations for hobbies or collections, such as coins and antiques, and fortunate is the pharmacist who has found that by turning to such activities he is resting his mind from the troubles of the day. But even more fortunate is the pharmacist who realizes that right within the province of his own profession there rest many possibilities for hobbies, the exercise of which will not only afford him relaxation, but increase his professional pride and knowledge and the scope of his work.

MEDICAL PIONEERS IN THE PERUVIAN AMAZON

By Edward A. Westphal, M. D.*

BEYOND the lofty ranges of the Andes Mountains, in the upper reaches of South America's vast Amazon basin, is one of the last great primitive frontiers of economic development in the Western Hemisphere. Here the second World War, with its insatiable demand for strategic materials, has given new impulse to regional development. In the forests and valleys sloping down to the Amazon lowlands are valuable resources of rubber, hardwoods, cinchona. Fertile stretches of land are adapted to tropical and semi-tropical agriculture. Oil has been discovered in this trans-Andean region. The Ganso Azul field south of Pucallpa, Peru, already is helping to supply the area's petroleum needs. The montana region, as it is popularly called in Peru, is on its way up economically.

For centuries, while other areas of the Americas moved forward in economic development, the upper Amazon region remained almost untouched. On one side the towering Andes walled it from access to world markets by way of the Pacific. And between the montana and the Atlantic lay more than 2,000 miles of tropical jungle, impenetrable to commerce except by navigation on the Amazon and its tributaries. Now the airplane has opened fast routes of communication. In addition, Peru is pushing penetration roads over the Andes. The spectacular Central Highway has been virtually completed from Lima to Pucallpa. Other penetration roads are under way or projected to the north and south. Agricultural experiment work proceeds with colonization. The pioneering settler finds in this Amazon country the promise of a new frontier which responds to the productivity of human labor, transportation and machinery.

And, in the vanguard of the pioneering work in the Peruvian Amazon, are doctors and sanitary engineers, applying modern medical techniques to the task of making the jungle country healthful and productive. Modern health work in the montana region has been expanded greatly in the last two years, as part of inter-American cooperation in health and sanitation activity. Peruvian doctors and engineers are working with doctors and engineers from the United

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States to increase the productivity of the Amazon country and improve the jungle environment for human habitation.

Peru was one of the first of the other Americas to join with the United States in cooperative health and sanitation work recommended by the Rio de Janeiro conference of American foreign ministers in 1942. Health and sanitation measures in Peru's trans-Andean region were undertaken in recognition of the potential importance of the area in expanding hemisphere production of tropical-grown materials, such as quinine and rotenone, as well as in its potential long-range value to the development of Peruvian economic resources. Development work in the Peruvian Amazon, including the health and sanitation program, is Peru's counterpart of similar development being carried out in the huge Amazon basin by Brazil, Bolivia, Ecuador, and Colombia. In the health work, particularly, inter-American cooperation plays a timely role in aiding the development of hemisphere resources.

The health program in Peru, like that in most of the other eighteen countries participating in the inter-American health and sanitation activity, is carried on by a special cooperative service organized as an agency of the Peruvian Government. This special agency is known as the Servicio Cooperativo Inter-Americano de Salud Publica, better known in Peru as the SCISP. The SCISP is an agency of the Peruvian Ministry of Health. The original agreement, signed in July, 1942, called for a two-year health program costing $1,000,000. This agreement has been extended over a five-year period, involving total projected expenditure of $3,000,000. To date the Institute of Inter-American Affairs has contributed $1,850,000 and the Peruvian Government $672,000 in cash, together with personnel, services and facilities equivalent to an additional $200,000.

Fourteen United States specialists, mostly specialists in tropical medicine and sanitary engineers, have been assigned to assist the SCISP by the Institute of Inter-American Affairs. The majority of the personnel are Peruvians. Nearly 800 Peruvian nationals are at work on SCISP's projects and in the administrative forces. Of these about 100 are professional personnel, including doctors, sanitary engineers, nurses, sanitary inspectors, nurses' aids and laboratory technicians.

When SCISP was created, it was charged by the Peruvian Government with the tasks of planning, organizing and putting into operation a medical program in Peru's upper Amazon region. Certainly

this was no small job. Despite considerable progress in opening air transport routes and highways over the Andes, communications were extremely difficult by comparison with more developed areas. SCISP doctors and engineers had to become accustomed to travel by foot and mule back, canoes and rafts on the rivers, in addition to airplane flights over uncharted jungles.

Still more troublesome was the problem of transporting materials and equipment for construction of hospitals and dispensaries. When SCISP began work in 1942, the Trans-Andean Highway to Pucallpa was incomplete. The submarine menace in the Caribbean and the South Atlantic was at its height. Peru's biggest Amazon trading city, Iquitos, is about 1200 miles up the Amazon from the Atlantic. Ordinarily heavy materials and equipment move into the upper Amazon by way of the Amazon from the Atlantic. With shipping scarce, however, it was necessary to transport materials over the mountains to Tingo Maria or to the Aguaytia River from Lima, thence to Yurimaguas or Pucallpa on rafts and by river steamer to Iquitos. A shipment sent in this fashion took from three to six months to arrive and part of the goods were damaged or lost. In the construction of the Yurimaguas Hospital many materials were shipped down the rapid-filled Huallaga River from Tingo Maria. Nearly 50 per cent of materials shipped in this way were lost. Two raftmen were drowned. But there was no other way of shipping at the time.

Now all materials are shipped by boat from Lima up the Pacific via the Panama Canal, to Iquitos, a distance of 10,000 miles, and then from Iquitos they are reshipped on river steamers to their destination. During the dry season supplies can be sent over the Pucallpa road as far as Pucallpa, then by river boat to Iquitos.

The program of medical assistance and preventive medicine being carried out in the jungle was the result of preliminary surveys and conversations with the officials of the Ministry of Health. In agreement with them, the following program was devised:

1. The construction and operation of combined hospitals and health centers in the larger and more strategically located cities.

2. The establishment of medical dispensaries in the smaller towns and villages.

3. The establishment of sanitary posts in the smaller settlements where a dispensary under the care of a physician was not economically feasible.

4. Setting up of a system of mobile units to render the same services to the population sparsely settled along the highways and rivers.

The center of this work is the city of Iquitos, a product of the rubber boom of the last century and once again a flourishing city of 50,000 inhabitants. The shipping and commercial center of the entire area, Iquitos, is located on the Amazon River, just below the union of the Ucayali and Maranon Rivers. Here the SCISP is constructing an addition to a small and inadequate existing hospital. The addition, which is larger than the old hospital, will supply this institution with 88 beds additional, and facilities for surgery, X-ray work, laboratory work, out-patient department, administration building, and kitchen and dining rooms. The SCISP also has been operating a general out-patient clinic for indigents in Iquitos where about 4,000 patients are treated and supplied with medicines monthly.

The SCISP placed in operation in Iquitos a health center in which emphasis is placed on preventive medicine work. This unit treats about 3,000 persons monthly. By preventive medicine is meant the treatment of transmissible diseases, such as malaria, tuberculosis, syphilis and hookworm, and searching out, treating and following up cases to eliminate carriers. This work also includes vaccinating against childhood diseases, typhoid, yellow fever, etc.; orienting mothers in the care and feeding of infants and children; instructing pregnant mothers in the care of themselves; educating the public to a knowledge of what constitutes good health and how to achieve it.

Iquitos is a training center for health workers. Courses in public health are given to new physicians entering the SCISP. Here, too, are trained sanitary inspectors who man Sanitary Posts. Visiting nurses are trained for health centers and nurses' aides for hospital work. Trainees from these courses are already in service at Pucallpa, Yurimaguas and Tingo Maria Hospitals, all built by the SCISP.

Other hospitals have been or are being built in San Martin and Satipo. Hospitalization, out-patient medical care, preventive medicine and health education generally are carried out in these hospitals. They have an average capacity for forty in-patients each and out-patient facilities. Built in towns with limited living and sanitary facilities, they must furnish living quarters for doctors, nurses and practically the entire hospital staff. They also have water supply, electric light and sewer disposal plants.

Locations were chosen so that these hospitals could serve as large an area as possible. Tingo Maria Hospital is in the most successful and rapidly expanding colonization project in Peru. It is the site of an important agricultural experimental station. Rubber and cinchona plantations are being developed in the area. Other important products of the area are tea, barbasco and lumber.

Pucallpa Hospital is located on the terminal of the Central Highway from Lima over the Andes to Huanuco, Tingo Maria and Pucallpa. It is an increasingly busy shipping point. Freight now is shipped over the road to Pucallpa and from there down the Ucayali to Iquitos by river boat. Pucallpa promises to become more important commercially when the highway is completed for all-year traffic. From Pucallpa, the upper Ucayali and much of the Urubamba River can be given medical attention. Moreover, Pucallpa is a station on air routes from San Ramon to Iquitos and Puerto Maldonado. The newly built highway has been a boon to the area.

Yurimaguas Hospital is located on the Huallaga River, on an important stop on the Chiclayo-Iquitos air line. The town is a large insecticide producing and shipping center. From it, the Huallaga River area below Tingo Maria receives medical care.

San Martin Hospital is built in one of the largest Peruvian Amazon jungle towns. The town has 8,000 inhabitants and 10,000 more in the immediate vicinity. It is the center of a tobacco and coffee growing area. From San Martin medical services for much of the Department of San Martin will be supplied. The San Martin and Yurimaguas region is due for further development when the highway to Bella Vista, on the Maranon River, is completed and extended to Yurimaguas and San Martin.

Satipo Hospital is in a colonization area second in importance only to Tingo Maria. It also has an agricultural experimental station. Progress of the town has been retarded by the prevalence of malaria, but has taken a decided upsurge with the establishment of a clinic, the construction of the hospital and the introduction of malaria control measures. Many colonists have moved into the area. Satipo produces cinchona, tea, tobacco, lumber, insecticides and other tropical products.

Each hospital treats on an average more than 2,000 patients a month in the out-patient clinic. The in-patient beds are always

filled. A staff of thirty or thirty-five is required to operate one of them.

Next in line in the chain of SCISP Amazon medical services are the dispensaries. These units are staffed by a physician, usually have a bed capacity for ten in-patients and do the same general work as is done in the larger hospitals. They are located in smaller towns and fill in gaps between the hospitals. They send their surgical patients to the nearest hospital. The SCISP has constructed dispensaries at Caballococha, in a rubber-producing section on the Amazon below Iquitos; at Gontamana on the Ucayali between Pucallpa and Iquitos, near which oil deposits are being developed; at Barranca, on the Maranon River above Iquitos. Other units are at Borja, on the navigable headwaters of the Maranon and terminal of a new highway under construction over the Andes; and at Requena, on the Ucayali, the center of another rubber area. In addition, the SCISP is operating dispensaries in rented facilities at Puerto Maldonado and Satipo.

Next are Dispensary Posts. These are under the care of a Sanitary Inspector, trained by the SCISP in Iquitos. They are located in villages where it is impractical to place a physician. The inspectors devote themselves mostly to rural educational work in preventive medicine and in the improvement of local sanitary conditions. They treat common local diseases and collect cases they are not able to treat for the regular visit of dispensary launches. The work of these Sanitary Inspectors is supervised by the physician in charge of the dispensary launch for the area. The launch supplies them with medicines. The inspectors are responsible for a section of river up to the area of the next Sanitary Inspector. They travel by canoe. The SCISP has 27 sanitary posts, including 12 on the Ucayali River, 2 on the Huallaga River, 3 on the highway between Tingo Maria and Pucallpa, 1 in the Madre de Dios area, 1 in Satipo area, 2 on the Amazon, 3 on the Maranon.

Last in the chain of medical services are the dispensary launches and mobile units on wheels. These perform the same functions as the other units but serve the more sparsely settled river population. Three launches are in operation which make regular trips permitting them to look after nearby areas. A wheeled unit operates on the highway between Tingo Maria and Pucallpa, treating colonists, highway, rubber and cinchona workers.

So much for the jungle proper. Several months after its creation, the SCISP also was assigned the job of carrying out the sanitation of Chimbote, an extremely malarious port north of Lima where harbor installations and industrial works are in progress. Here the SCISP is draining malaria swamps, installing a water supply and distribution system, building sewage disposal facilities and building a hospital and health center.

Specially trained personnel are needed for SCISP projects. For training of physicians in preventive medicine and of visiting public health nurses, the SCISP is building a health center in the Rimac District of Lima. This center also will serve as a demonstration unit. The SCISP, through the Institute of Inter-American Affairs, is sending doctors, nurses and engineers to the United States for public health training. Seven physicians, two nurses, two sanitary engineers and one public health educator have been sent for training in United States universities. They are committed to continue working for the SCISP after their return to Peru.

Contrary to what many people believe, the jungle is not an unhealthful place. With a little knowledge and proper precautions, one may live quite healthfully in the jungle. Treatment of disease is but a small part of the work necessary to make the Amazon jungle healthful for economic development. Disease treatment is only a palliative. The health work aims mainly at the elimination of disease at its source. This means that each hospital and dispensary must be a center from which the community is educated in the prevention of disease and for control measures designed to eliminate such disease carriers as mosquitoes, flies, contaminated water.

The most common and harmful disease of the jungles is intestinal parasitosis, chiefly hookworm. In surveys we have found that at least 95 per cent of the patients suffer from intestinal parasitosis. This is due to the lack of toilet facilities and non-use of shoes. Hookworm is transmitted by stepping on contaminated soil. Children suffering from hookworm are thin and pale and pot-bellied. Many die from enemies. Much educational work needs to be done before hookworm is controlled.

Other common diseases are malaria, tuberculosis, yaws, tropical ulcers, venereal diseases, leprosy and leishmaniasis. Most of these can be prevented by proper precautionary measures and knowledge. Most of the jungle inhabitants are undernourished, making them easy

prey to disease. They live on a salted dry fish called "Paiche," yuccas (manioc root) and bananas. They need to be taught to eat properly but changing dietary habits is difficult.

In Tingo Maria people at first were unfamiliar with the health program. Now there is a marked change. Privies and safe wells for drinking water are being built. More children are wearing shoes. The general health level is rising. Tropical ulcer and leishmania have almost disappeared. The same is happening in varying degrees in other localities. Satipo has many new colonists moving in as malaria decreases. The hospital inspires a feeling of security. We like to think that the increased tempo of progress is in part, at least, due to the hospitals and the improved sanitation.

The work by the SCISP is but a small fraction of that being done by the Ministry of Health in Peru. The SCISP is temporary and is dedicated only to the jungle and to Chimbote. An indication of the increasing amount of overall health work being done by the Health Ministry can be found in its budget. In five years this has increased from a round 3,000,000 soles to more than 20,000,000 soles.

What is being done in the jungle is but a beginning, adapted to local conditions and the economic means available. More needs to be done before the Amazon area, with its potential riches, becomes completely safe for economic development. But the hemispheric cooperative health program started by the Rio conference provides a basis for expansion of the work and a beacon for the future in Amazon development.

SENECIO PLATYPHYLLUS

An Old Native Russian Medicinal Plant and Its New Alkaloidal Drug Platyphylline Bitartrate

By Edgard Yan Allen, M. Sc.

AMONG the numerous native Russian plants which are used for medicinal purposes is one known as "Krestovnick shirokolystny" or Senecio platyphyllus in Latin. This member of the Compositæ family is indigenous to the "Kavkaz" or Caucasus region of Russia. It is a large grassy perennial plant having large reniform or almost triangular leaves with yellow flowers contained in an involucre.

In the leaves and roots of this herb, which is collected in August and September, is contained the alkaloid "platyphylline," which possesses atropine-like properties when employed therapeutically. The root of this plant is used more extensively than the leaves. This herbaceous perennial is utilized by the inhabitants of Kavkaz for its antispasmodic and analgesic action. Due to these attributes, it attained prominence and is now considered as being an old Rusian folk remedy.

Prescriptions which were written for this drug plant usually read as follows: (1)

℞ Tincturæ Senecio platyphylli 30.0 Gm.
S. 30-40 drops 2-3 times a day.

As platyphylline is able to replace atropine in optical medical practice, the following formula was prescribed:

℞ Sol. Platyphyllini 1% 10.0 Gm.
S. Eye drops 1-2 drops.

Recently attention has once more been focused upon this medicinal plant. This is due to the fact that a new salt of the alkaloid platyphylline has been discovered. This substance is platyphylline bitartrate $C_{18}H_{27}NO_5C_4H_6O_6$. It is a white crystalline powder soluble in ten (10) parts of cold water (15° C.), in five (5) parts of hot water, and in forty-two (42) parts of hot alcohol.

When used in the form of eye drops a one per cent (1%) solution is employed. It is used internally as a powder in 0.002 Gm.

doses or ten (10) drops of a 1 : 500 solution to be taken three (3) times a day. Intracutaneous injections are made using 1-2 ml. of a 1 : 500 solution of this medicinal. It is utilized in the form of suppositories in quantities ranging from 0.0015-0.0030 Gm. 2-3 times a day.

The action of platyphylline is very similar to atropine. It rapidly produces a considerable dilation of the pupil of the eye. However, this action lasts for a short period of time (maximum duration: 24 hours). It exhibits little influence on accommodation. It is used in cases of seasickness or airsickness, or in consistent vomiting as in cases of pregnancy (reduces stomach spasm). Platyphylline diminishes muscular spasm of the intestines. It is used in the form of suppositories for painful hemorrhoids. (2)

This medicament is prescribed in modern Russian pharmaceutical practice as follows: (3)

℞ Sol. Platyphyllini bitartarici 1% 10.0 Gm.
D. S. Eye drops.

℞ Platyphyllini bitartarici 0.002 Gm.
Sacchari albi 0.20 Gm.
M. F. pulv. D. t. d. No. 6.
S. One powder three (3) times a day.

℞ Platyphyllini bitartarici 0.04 Gm.
Aq. destil. 20.00 Gm.
M. D. S. Ten (10) drops two (2) times a day before meals.

℞ Platyphyllini bitartarici 0.0015 Gm.-0.0030 Gm.
Oleum Theobromatis q. s.
M. F. Suppositorium.
D. t. d. No. 10.
S. One (1) suppository two (2) times a day.

Notice: In Russian pharmaceutical and medical practice it is customary to prescribe the largest single dose that may be safely administered. The above formulæ have been devised in accordance with this practice.

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SELECTED ABSTRACTS

Aluminum Phosphate Gel in the Treatment of Peptic Ulcer. Jacob Lichstein, M. D., Samuel Simkins, M. D., and Mitchell Bernstein, M. D. (Jewish Hospital, Philadelphia, Pa.). *Am. J. Digestive Diseases 12* (3): 65-69 (1945). The effects of aluminum phosphate gel on peptic ulcer were studied in 22 patients; one group of 15 with bleeding peptic ulcer and another group of 7 with uncomplicated peptic ulcer. A third group of 15 additional patients, serving as controls, were treated with the usual ulcer regimen.

Aluminum phosphate gel produced rapid marked roentgenographic improvement and cure in a much higher percentage than did the usual ulcer regimen with or without aluminum hydroxide gel. The aluminum phosphate gel produced prompt relief of ulcer pain, had an excellent effect on appetite and return of strength, and was much less constipating than the aluminum hydroxide gel. There was a moderate reduction of free hydrochloric acid and total acidity. There was no change in mineral metabolism as measured by the blood calcium and phosphorus, nor was there any effect on the increase of the blood urea nitrogen commonly observed in bleeding peptic ulcer.

The erythropoietic response following bleeding peptic ulcer is determined by the degree of the anemia at the moment and is independent of the initial severity of the hemorrhage itself.

Fatal Agranulocytosis Resulting From Thiouracil. M. I. Ferrer, D. M. Spain and R. T. Cathcart. *J. A. M. A. 127,* 646 (1945). The authors briefly review the reports of other observers on the use of thiouracil in the treatment of hyperthyroidism and describe a fatal case of agranulocytosis following the use of thiouracil, with the postmortem findings and microscopic examination.

The patient weighed 97 pounds on admission and was extremely emaciated. A diagnosis of hyperthyroidism was made, and iodine therapy was tried without avail for fifteen days. Administration of

thiouracil was then begun; the dosage was 0.2 gm. four times a day for the first three days, and for the remainder of 131 days of hospitalization it was increased to 0.3 gm. at the same frequency.

The patient's condition had improved markedly at the time of his discharge to the outpatient department; his weight had increased to 124 pounds, and for thirteen weeks prior to this time the pulse rate had averaged 80 and the white blood cell count had ranged from 5,100 to 7,400.

During a period of more than a month in the outpatient department the patient received a single daily maintenance dose of thiouracil, 0.9 gm. at first and 0.6 gm. later, and his health seemed excellent. Upon the observation at this time that his white blood cell count had decreased to 1,250 with 37 per cent polymorphonuclear leukocytes, he was once more hospitalized.

Within a few days the temperature reached 105° F. and severe pharyngitis developed. The white blood cell count continued to decrease, reaching 450 with no granulocytic cells on the seventh hospital day, at which time death occurred. Blood transfusions, the intramuscular administration of Pentnucleotide, and penicillin were of no avail.

It is believed that agranulocytosis resulting from thiouracil is attributable to the development of sensitivity or idosyncrasy to the drug, rather than a cumulative effect. The postmortem finding of hemoglobin casts in the renal tubules in this case is believed to be accounted for on the basis of transfusion reactions exhibited by the patient, although other observers have reported renal complications following thiouracil therapy. Since the drug is soluble at pH 8.5 and is closely related to the sulfonamides, it has been suggested that the concurrent administration of sodium bicarbonate is advisable.

Administration of Penicillin by Mouth. Preliminary Report. P. György, H. N. Vandegrift, W. Elias, L. G. Colio, F. M. Barry and J. D. Pilcher. *J. A. M. A 127,* 639 (1945). The published reports of other investigators that trisodium citrate was found to be a suitable buffer for penicillin when the latter drug was administered orally led the authors to make clinical studies on this combination.

Twenty-three cases of gonorrhea, most of which were resistant to sulfonamides, were successfully treated by the oral administration

of buffered penicillin. For children the dose of penicillin was 10,000 units every three to four hours; for adults, from 15,000 to 40,000 units every three hours. The amount of trisodium citrate given was from one to five grams per dose. All cases were cured in from one to three days.

In three additional cases of gonorrhea in children the oral administration of a total of 200,000 to 300,000 units of penicillin buffered as described above produced only temporary cure. The treatment was repeated twice with identical temporary results. In contrast, the same doses (10,000 units every three hours) given intramuscularly resulted in permanent cures.

Three cases of gonorrheal conjunctivitis in infants were rapidly and permanently cured by penicillin and sodium citrate given by mouth in a dosage similar to that previously mentioned; the total amount of penicillin required ranged from 140,000 to 200,000 units.

In one case of chronic otitis media accompanied by suppuration, a complete cure was produced by the oral penicillin and sodium citrate combination, although a prolonged treatment with sulfathiazole had proved ineffective.

One patient with early acquired syphilis and positive dark field examination received oral doses of 30,000 units of penicillin and 5 grams of sodium citrate every three hours. The dark field examination was negative after thirty hours. At the end of the second day the mode of administration was changed to the standard intramuscular technic.

Studies on the blood levels of penicillin following the administration of the calcium salt to children revealed that when the drug was given by mouth thirty minutes before breakfast, the simultaneous administration of sodium citrate increased the absolute blood levels and also prolonged its retention there.

Sulfonamide Therapy in Gonorrhea: Results in 210 Cases. H. Gorenberg and P. Shulman. *U. S. Naval Med. Bull. 44,* 596 (1945). In a series of 210 cases of gonorrhea treated with sulfathiazole, sulfadiazine, or both, a striking difference between white and Negro patients was noted in response to treatment.

Initially, a daily total of 8 gm. of the sulfonamide was given in 4 doses; this was later decreased by one-half, since the larger dosage

produced no increase in the percentage of cures. Treatment was continued over a seven to ten day period, after which the patient was placed under observation for two or three weeks. The absence of, or a negative, urethral discharge after three weeks was considered as indicative of a cure.

Apparent cure was observed in only 55.5 per cent of the 173 white patients, in contrast to the figure of 86.5 per cent among the 37 Negroes treated. The percentage of cures was higher among patients who were hospitalized than among those who received ambulatory treatment.

Sulfadiazine therapy was tried in 41 cases which failed to respond to sulfathiazole, but the former drug produced an apparent cure in only 26.8 per cent of these. The results obtained in 17 cases who were started on sulfadiazine were disappointing; only 22 per cent of the white patients responded to treatment, although 62.5 per cent of the Negroes treated were apparently cured.

Polyvinyl Alcohols as Blood Substitutes. N. W. Roome, L. Ruttle, L. Williams and W. Smith. *Canad. M. A. J. 51,* 293 (1944); through *U. S. Naval Med. Bull. 44,* 548 (1945). The polyvinyl alcohols available commercially are offered in a number of grades, each of which consists of a mixture of macromolecules of various sizes as a result of polymerization to different degrees. They are a series of water-soluble colloids whose properties vary with the average molecule size.

Polyvinyl alcohol RH623 possesses essential physical properties closely resembling those of the plasma proteins. In tests on dogs which had suffered acute hemorrhage, it was as effective as similar blood transfusions in maintaining the blood pressure, and did not appear antigenic. It is lost from the blood stream in dogs at about the same rate as the plasma proteins regenerate.

The disadvantages of the polyvinyl alcohols as blood substitutes are: (1) they do not promote wound healing, or act as foodstuffs, as a protein might; (2) they do not aid hemostasis by clotting; on the contrary, large amounts may be expected to impede clotting because of dilution of the fibrinogen; (3) they cannot provide antibodies and erythrocytes, and thus are valueless in anemias and in infections, except for improving the peripheral circulation.

The non-protein nature, however, may be advantageous in reducing the likelihood of anaphylactic reactions. The low cost, ease of preparation, and stability in storage are other advantages of this type of polyvinyl alcohol. The authors believe it to hold promise as a first treatment for hemorrhage or shock, provided that hemostasis can be obtained or that direct bleeding is not a prominent feature.

Maintenance of the Blood Level of Penicillin After Intramuscular Injection. W. M. Parkins, M. Wiley, J. Chandy and H. A. Zintel. *Science 101,* 203 (1945). The use of specially prepared ossein gelatin in either a 6 or 20 per cent concentration in saline solution which also contained a long-acting vasoconstrictor was found to maintain the blood concentration of penicillin at measurable levels for seven to eight hours following single intramuscular injections in both unanesthetized dogs and human patients. The combination of both gelatin and a vasoconstrictor was more effective than either substance alone for this purpose.

The solutions employed contained either 5,000 or 10,000 Oxford units of penicillin sodium per ml. and either 0.025 or 0.005 per cent of "Privine Hydrochloride" or "Neo-synephrin Hydrochloride." Either vasoconstrictor was administered to dogs, but only the latter was given to the human subjects. The dosage of penicillin was either 1,000 or 2,000 units per kilogram for dogs and approximately 1,000 units per kilogram for human patients.

Blood samples were assayed for penicillin concentration one-half hour following injection and thereafter at one-hour intervals for eight hours. It was observed that through the use of the technic described three intramuscular injections per day sufficed instead of eight, as ordinarily performed, and with less variation in the blood level of the drug.

The authors state that while this paper was in press other investigators reported observations on the prolongation of penicillin blood levels by adrenalin. A few experiments on gelatin and adrenalin in combination were undertaken, with the result that blood levels of penicillin were maintained up to six and seven hours.

SOLID EXTRACTS

Corn is the greatest United States crop. Last year 3,228,361,000 bushels were grown. This would fill a train of freight cars reaching half way around the earth. Twenty per cent of the corn is used industrially, the balance is fed to chickens and farm animals. Even penicillin production depends on corn due to the use of corn steep liquor in its nutrient broth.

AJP

Cancer research stands today on the threshold of new and great advances. It has already given us ways of producing and of controlling the production of the disease in laboratory animals. It has begun to give us knowledge of how cancer cells differ from normal cells. Best of all, at least for the time being, is the increasing knowledge of how to recognize danger signals indicating the presence of cancer.

According to the American Cancer Society, there are now 17,000,000 living Americans who will die of cancer unless something is done, and there are at least 5,500,000 of them who can be saved from death if the danger signs are recognized and simple, direct action taken. Education, financial resources and courage are needed in the advancing fight against this disastrous malady.

AJP

A single injection of a new type of penicillin—penicillin X is reported to cure gonorrhea in 94 per cent of the cases tried. This is indeed a far cry from the days of oil of sandalwood and the other feeble urinary antiseptics that often made treatment require months of therapy.

AJP

In sixteen years 723 patients have been admitted to the National Leprosarium at Carville, La. Of this number 20 per cent have been released with the disease arrested. Two new drugs, Promin and Diasone, seem to be of value in the treatment of the disease.

Another serious health problem, little recognized, is rheumatic fever and the sometimes resultant rheumatic heart. These are the chief killers of children, and they stab their way into the ranks of the adults, too. Current statistics show that about 20 per cent of the men rejected by the Army and the Navy for physical reasons were suffering from rheumatic heart disease. About 40,000 service men have contracted it while fighting in the jungles. Among school children from 5 to 14 years of age, one of every hundred is attacked by the illness, which, if not caught in time, leaves its irremovable marks. Unfortunately, the symptoms of rheumatic fever in children are often mistaken for "growing pains" and other childhood complaints of little consequence, and, hence, go unheeded. The problem is so acute that the Federal Government is using considerable sums of money in the various States to bring the disease to the fore and to instigate educational programs and therapeutic measures so that future generations will not have this terrific mortality and disability.

AJP

Copper was man's first useful metal. It is thought to have been found in the neolithic age, perhaps as early as 13,000 B. C.

AJP

The mass of the sun has been computed as 2 times 10 to the 27th power, or 2,000,000,000,000,000,000,000,000,000 tons, and its radiant energy as 12 times 10 to the 13th power, or 120,000,000,000,000,000 tons per year.

AJP

When Philadelphia was the Nation's capital in 1793, it experienced an epidemic of yellow fever which killed more than 4000 persons in a period of four months, representing one-tenth of the city's population at that time.

BOOK REVIEW

Organic Chemistry, With Applications to Pharmacy and Medicine. By Eldin V. Lynn, Ph. D., Professor of Chemistry, Massachusetts College of Pharmacy, Boston. Second edition, thoroughly revised. Lea and Febiger, Philadelphia, 1945. Octavo, 355 pages, including index. Price: $4.50.

Since the first edition of this work appeared in 1941 there have been numerous additions to the medical armamentarium, particularly of synthetic organic compounds. Numerous drugs which were at that time described in New and Nonofficial Remedies have since received official recognition; others have been dismissed either from the official books or the N. N. R.; and still others have only recently been accepted by the N. N. R.

Without altering markedly the general plan or scope of his text, the author has brought it up-to-date by making such additions or changes as were thus indicated. The second edition has continued the aim of the first, i. e., to present the fundamental principles of organic chemistry, illustrated especially by compounds important in pharmacy and medicine, both to students taking a first course in organic chemistry and to those taking a more advanced course emphasizing the medicinal substances. The author has avoided the attempt to teach chemicals in place of chemistry; yet, in the opinion of the reviewer, a more complete discussion of the medicinal chemicals included would greatly increase the value of the book to the student of pharmacy.

By reducing the size of the margins the printer has succeeded in compressing into 355 pages the same amount of text material that required 410 pages in the first edition. The quality of paper used in the second edition is inferior to that of the first, doubtless because of war-time conditions.

Among the titles of official substances added to the second edition may be mentioned the following: Propylene Glycol, Glyceryl Triacetate, Diethylstilbestrol, Methyl Parahydroxybenzoate, the official sulfonamides, Pamaquine Naphthoate, Quinacrine Hydrochloride, Picrotoxin, and Resorcin Brown.

Among the non-official substances now mentioned are Iodostarine, Sodium r-Lactate, Calcium Levulinate, Zephiran Chloride, Phemerol, Ceepryn, Aerosol O. T., Merphenyl Nitrate (also Borate and Picrate), Octofollin, Phenarsone Sulfoxylate, Fuadin and several other organic antimonials, Amylcaine Hydrochloride, Triphal, Biotin, Demerol, Diodoquin, Penicillin and several other antibiotic agents, Sulfapyrazine, Sulfamerazine, Dimazon, Digitalin German, Digitaline Nativelle, Gitalin, Digilanid, Scillaren, and Urginin. Any of the above which have been accepted by the N. N. R. are so designated.

Several compounds now recognized as official reagents are identified as such. Various other organic compounds of industrial importance, e. g., the acetates of the glycols, cellosolves and carbitols, glyceryl monostearate, dioxane, etc., now receive mention.

A rather rapid perusal of the book revealed only a few minor errors; e. g., the titles concerned should be corrected to read as follows: Theophylline Ethylenediamine (page 129) and Benzosulfimide (page 234), and Estrone should be designated as U. S. P., not N. N. R. (page 256).

The logical arrangement of the material used in the first edition has been altered only very slightly. The organic compounds are considered by classes, under each of which are presented the nomenclature, preparation, properties and reactions of compounds of this group. Following this is a brief discussion of the important medicinal substances belonging to the class of compounds under discussion.

Although it would seem necessary for the lecturer to amplify the text material presented on many of the medicinal chemicals, this textbook should continue to serve a useful purpose in presenting organic chemistry to the student of pharmacy or medicine.

A. A. Dodge.

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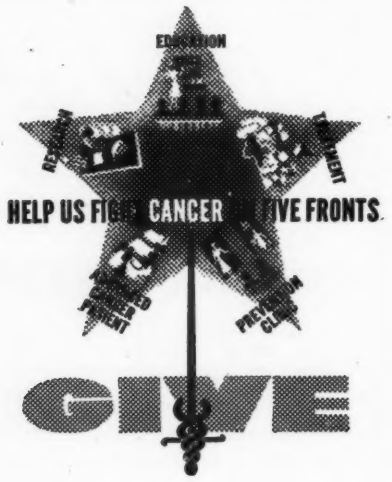

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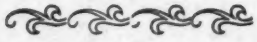

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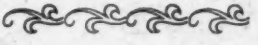

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